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Palladium-Catalyzed α -Arylation of Carboxylic Acids and Secondary Amides via a Traceless Protecting Strategy

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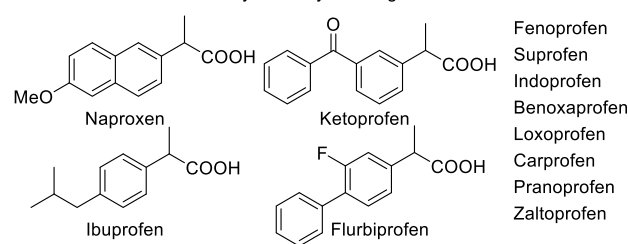
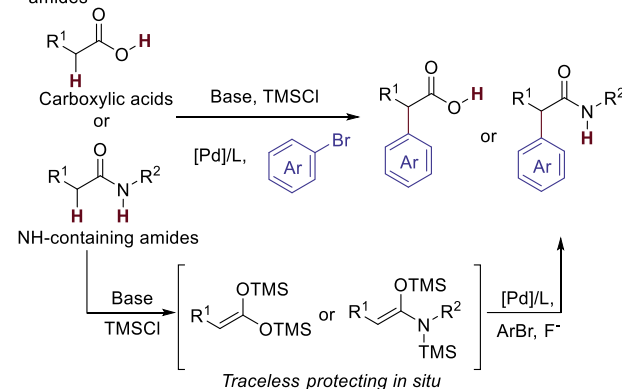
Supporting Information

ABSTRACT: A novel traceless protecting strategy is presented for the long-standing challenge of conducting the palladium-catalyzed α -arylation of carboxylic acids and secondary amides with aryl halides. Both of the presented coupling processes occur with a variety of carboxylic acids and amides and with a variety of aryl bromides containing a broad range of functional groups, including base-sensitive functionality like acyl, alkoxycarbonyl, nitro, cyano, and even hydroxyl groups. Five commercial drugs were prepared through this method in one step in 81–96% yield. Gram-scale synthesis of medication Naproxen and Flurbiprofen with low palladium loading further highlights the practical value of this method.

Palladium-catalyzed α -arylation reactions are used for a range of applications.¹ However, the direct α -arylation of free aliphatic carboxylic acids, one of the simplest carbonyl derivatives and most common derivative in the carboxylic acid oxidation state, has not been developed. Likewise, the α -arylation of common, secondary amides, which contain an acidic N–H bond, has not been reported.¹ Instead, the α -arylation of esters, often serving as masked carboxylic acids, and of tertiary amides containing a narrow range of groups on nitrogen have been reported.^{2,3} However, the carboxylic acid, primary amide or secondary amide is often the desired product. Thus, the acid is converted to an ester prior to α -arylation and then converted back to the acid after this catalytic process, and amides must similarly be manipulated to generate α -aryl secondary amides by this catalytic process. For example, the synthesis of the Profen drugs by α -arylation involves both installation and removal of the ester groups (Scheme 1a), and the synthesis by classical methods is often even longer.⁴

The absence of direct α -arylation of carboxylic acids and NH-containing amides stems from the strong coordination of carboxylates and amidates to transition metals,⁵ the high pK_a value of α -CH bonds of carboxylates,⁶ and competing C–N coupling of the amidates.⁷ Three sets of α -arylations of α -aryl carboxylic acids have been reported, but these reactions have occurred with limited tolerance of functional groups and, most important, were limited to carboxylic acids containing an existing α -aryl group that enhances the acidity of the α -position or acetic acid as both substrate and solvent at a high 130 °C reaction temperature.⁸ Likewise, the few prior α -arylations of amides containing an N–H bond were limited to

Scheme 1. Selected Commercial Drugs Containing Free Carboxylic Acids and Our Design

a. Selected commercial α -aryl carboxylate drugsb. Our solution to the α -arylation of carboxylic acids and NH-containing amides

- Novel solution to two long-standing challenges
- Wide tolerance of nitro, cyano, acyl, alkoxycarbonyl, hydroxyl groups
- One-step synthesis of five commercial drugs
- Gram-scale synthesis outside a glovebox with low [Pd] loading

oxindoles for which the pK_a value of the α -CH bond is similar to that of the N–H bond.⁹

We considered that the conversion of carboxylic acids and secondary amides to the corresponding disilyl intermediates could lead to reaction of an aryl halide at the α position with a palladium catalyst. However, this strategy confronts several challenges. First, the synthesis of the di-TMS protected carboxylic acids or secondary amides must not require purification prior to use in the coupling with aryl halides because purification of the enolate reagent would be an extra step and purification of the labile disilyl ketene acetals could be difficult. Thus, any remaining reagents or byproducts and the solvent used to form the reagent must be tolerated by the

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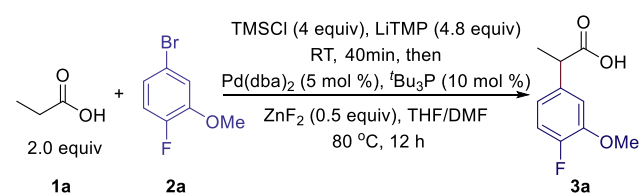
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coupling reaction. Second, the disilyl reagents contain two nucleophilic centers, one at carbon and one at oxygen or nitrogen, leading to potential interfering C–O or C–N coupling. For such reasons, the intermolecular coupling of aryl halides with an aliphatic carboxylic acid or secondary amide under mild conditions has not been reported.

Here, we describe a broadly applicable protocol for the palladium-catalyzed α -arylation of both carboxylic acids and secondary amides via a traceless protecting strategy involving *in situ* installation of silyl groups on the carboxylate or amide under basic conditions and subsequent palladium-catalyzed α -arylation with zinc fluoride as an additive (Scheme 1b). The practical value of this method is shown by a one-pot, gram-scale synthesis of Profen drugs with low catalyst loadings, as well as the tolerance of a broad range of functional groups in both aryl and heteroaryl halides.

We began our study to achieve the α -arylation of carboxylic acids by evaluating a series of reagents that could transiently protect the carboxylic acid *in situ* (Table 1). The reaction of

Table 1. Studies on Reaction Development^a



| Entry | Variation from the above conditions | Yield (%) ^b |
|-------|---|------------------------|
| 1 | none | 52 |
| 2 | no TMSCl | N.D. |
| 3 | TMSOTf, or TBSCl, or TESCl, or TBDPSCl instead of TMSCl | N.D. |
| 4 | LDA, or LiNCy ₂ instead of LiTMP | 7–40 |
| 5 | 50, or 65, or 90 °C instead of 80 °C | 30–40 |
| 6 | 1a (2.5 equiv), TMSCl (6 equiv), LiHMDS (5.3 equiv) | 92 (89) ^c |

^aReactions were conducted on 0.1 mmol scale of 2a. ^bDetermined by crude ¹⁹F NMR. ^cIsolated yield in parentheses. N.D., not detected.

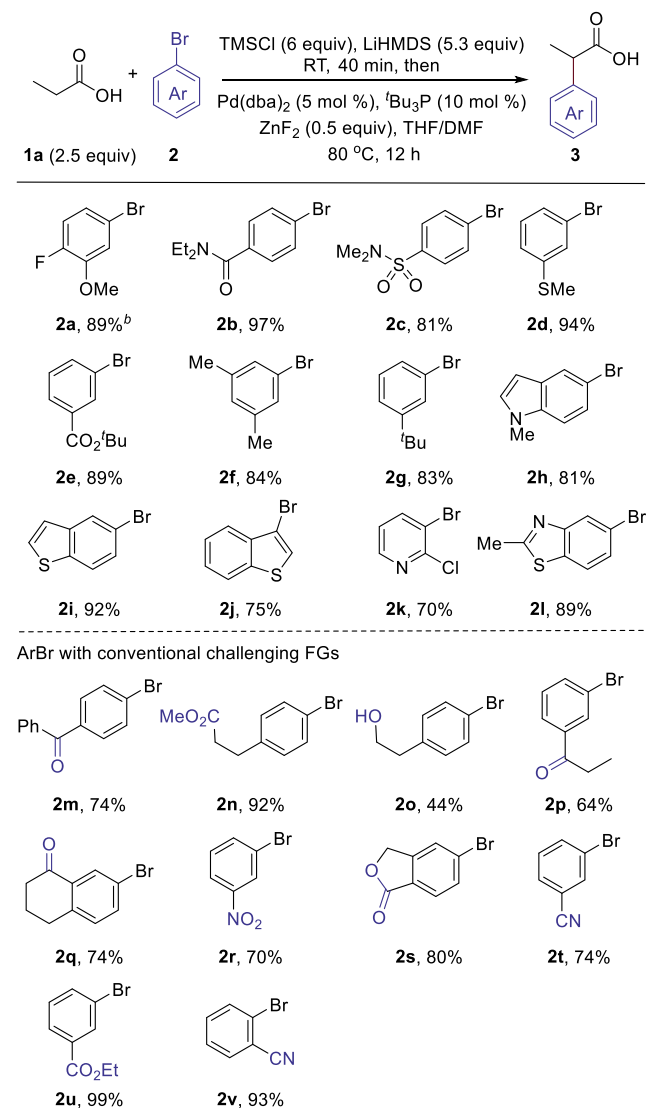
propionic acid (2 equiv) with the combination of trimethylsilyl chloride (TMSCl, 4 equiv) and lithium tetramethylpiperidide (LiTMP, 4.8 equiv) followed by addition of Pd(dba)₂ (5 mol %) and tBu₃P (10 mol %) as catalysts with a ZnF₂ (0.5 equiv) additive^{2c} formed the α -arylated product 3a in 52% yield (entry 1). The same reaction without TMSCl (entry 2), and the same reaction with other silyl groups, such as those from trimethylsilyl trifluoromethanesulfonate (TMSOTf), *tert*-butyldimethylsilyl chloride (TBSCl), triethylchlorosilane (TESCl) and *tert*-butyl(chloro)diphenylsilane (TBDPSCl), gave no detectable 3a (entry 3). Changes to the temperatures and use of other hindered alkylamide bases led to lower yields (entries 4 and 5).

After a series of evaluations of phosphine ligands, sources of palladium, alternative classes of bases, and additives at varying temperatures (see SI for a description of these experiments), the α -arylation product 3a formed in 92% yield by crude ¹⁹F nuclear magnetic resonance (NMR) spectroscopy and was isolated in 89% yield as the methyl ester with lithium bis(trimethylsilyl)amide (LiHMDS) as the base (entry 6). Thus, the conditions forming 3a in the highest yield consisted of the combination of propionic acid 1a (2.5 equiv), TMSCl (6 equiv), LiHMDS (5.3 equiv), Pd(dba)₂ (5 mol %), tBu₃P (10

mol %) and ZnF₂ (0.5 equiv) in tetrahydrofuran/dimethylformamide (THF/DMF) at 80 °C for 12 h.

This palladium-catalyzed α -arylation of carboxylic acids occurred with aryl bromides containing a broad range of functional groups at varying positions (Table 2). Both

Table 2. Scope of Aryl Bromides that Couple with Propionic Acids^a



^aIsolated yields after conversion to corresponding methyl esters for easy purification. ^b96% yield by ¹⁹F NMR was observed with only 1 mol % [Pd]; 1 mol % Pd(tBu₃P)₂ gave 87% yield by ¹⁹F NMR.

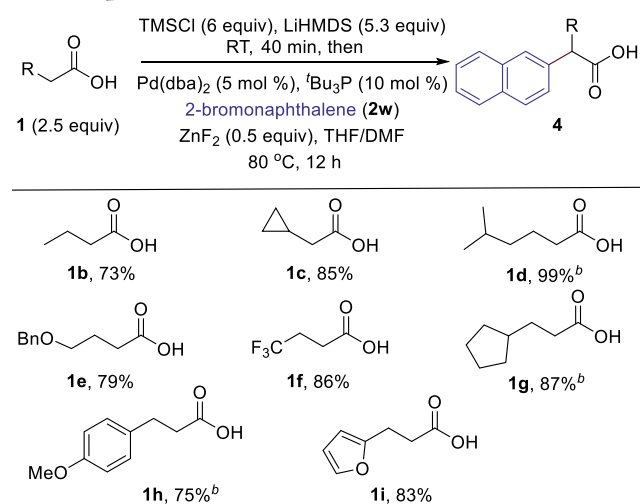
electron-withdrawing (amide in 2b, sulfonamide in 2c, ester in 2e) and electron-donating substituents (thioether in 2d, alkyl group in 2g) were well tolerated, giving arylated product in 83–97% yield. Aryl bromides containing multiple substituents underwent coupling in 84–89% yield (2a, 2f). The coupling of a range of heteroaryl bromides, such as bromo-indole, -benzothiophene, -pyridine and -benzothiazole, with propionic acid also occurred in high yield (2h–2l). Reactions with 1 mol % [Pd] instead of the standard 5 mol % occurred; for example, a high 96% yield of product 3a under this condition was measured by ¹⁹F NMR spectroscopy, and

the same reaction with 1 mol % of the preformed catalyst $\text{Pd}(\text{tBu}_3\text{P})_2$ gave a comparable 87% yield of **3a**.

During prior studies on the α -arylation of reactants having high pK_a values, such as esters and amides, in which excess of strong base was used to generate the enolate, the α -arylation was shown to be incompatible with aryl bromides bearing base-sensitive functional groups, such as acyl, cyano, nitro, etc.^{2a-c,3a,b} Similar to the reported coupling of the silyl enolates of esters,^{2a,e,g} the current method for the direct α -arylation of carboxylic acids overcomes this limitation; for example, it occurs with aryl bromides containing acyl, alkoxycarbonyl, cyano and nitro groups, giving the coupling product in 70–99% yield (**2m**, **2r–2v**). Aryl bromides containing hydrogens alpha to a carbonyl group (ester in **2n**, ketone in **2p** and **2q**) underwent the coupling process with the disilyl-substituted acid **1a** without reaction at this ancillary α -hydrogen (64–92% yield). Even a free alcohol in the aryl bromide was tolerated; the reaction of alcohol **2o** afforded the product in moderate yield.

Experiments on the α -arylation of a series of carboxylic acids are summarized in Table 3. Carboxylic acids containing linear

Table 3. Scope of Carboxylic Acids with 2-Bromonaphthalene as Substrate^a

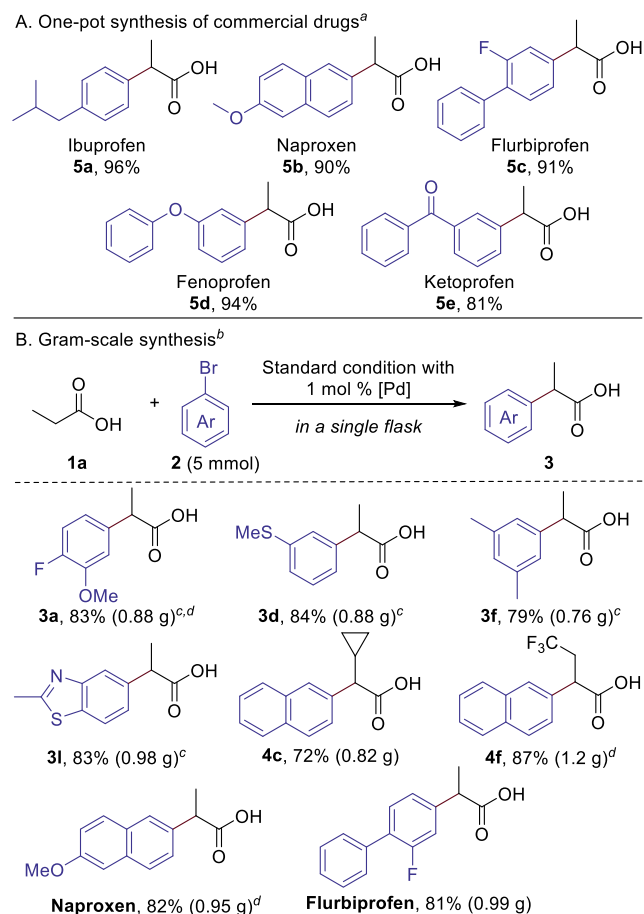


^aIsolated yield of product as carboxylic acid. ^bIsolated yield after conversion to corresponding methyl esters.

alkyl groups (**1b**, **1d**), cycloalkyl groups (**1c**, **1g**), alkoxy (**1e**) and CF_3 groups (**1f**) reacted in 73–99% yield. Carboxylic acids substituted with both aryl (**1h**) and heteroaryl (**1i**) groups on the α -carbon reacted, delivering the α -aryl carboxylic acid products in 75% and 83% yield, respectively. Acids containing two alkyl groups on the α carbon did not react.

To highlight the synthetic efficiency created by the present method, five commercial anti-inflammatory drugs were prepared in one step in high yield (Table 4A). For example, the well-known, nonsteroidal anti-inflammatory drug (NSAID) Ibuprofen has been prepared commercially in 6 steps (Boott process) or 3 steps (Hoechst process) from *iso*-butylbenzene.¹⁰ The reaction reported here forms the product in 96% yield in a single step by the developed α -arylation of propionic acid with 1-bromo-4-*iso*-butylbenzene. Similarly, Naproxen, Flurbiprofen, Fenopropfen and Ketopropfen, all were synthesized in one step in over 80% yield (**5b–5e**).

Table 4. One-Step Synthesis of Commercial Drugs and Gram-Scale Tests with Low [Pd] Loading

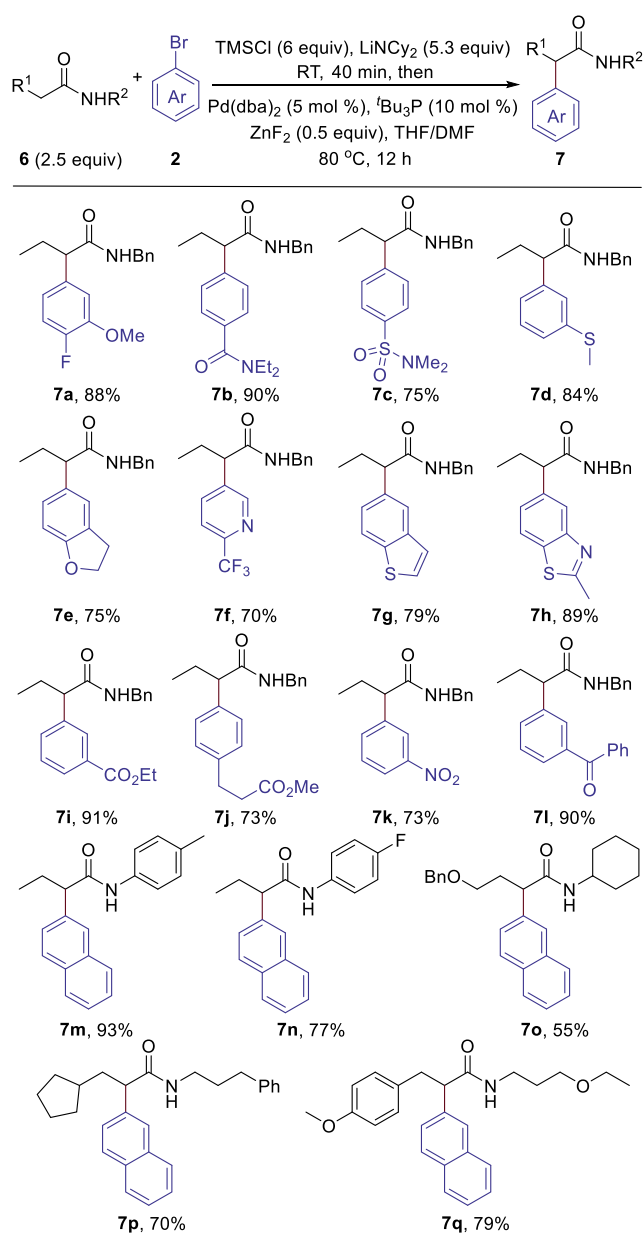


^aStandard condition as Table 1, entry 6. ^bSee SI for details. Isolated yield. ^cIsolated yield after conversion to corresponding methyl esters. ^d2 mol % [Pd] was used.

A series of gram-scale (5 mmol) couplings of aryl bromides with carboxylic acids underscore the convenience and synthetic value of our method (Table 4B). All reactions were conducted in a single flask under nitrogen outside a glovebox with 1–2 mol % [Pd] loading, instead of the 5 mol % used for the assessment of reaction scope. The aryl bromides **2a**, **2d**, **2f** and **2l** coupled with carboxylic acid **1a** in yields (79–84%) that were comparable to those obtained from reactions on a 0.1 mmol scale. The coupling of 2-naphthyl bromide with a series of carboxylic acids also occurred in high yields on gram scale, in this case to give compounds **4c** and **4f** in 72% and 87% yields, respectively. Finally, the synthesis of Naproxen and Flurbiprofen occurred in one-step on gram-scale in over 80% yield.

The approach to the α -arylation of acids also was applicable to the α -arylation of amides containing NH-bonds with minor modification of the base. The reaction of *N*-benzyl butyramide (**6a**) was chosen as the model substrate. Under the standard conditions described for the reactions of carboxylic acids (*vide supra*), only 14% of α -aryl amide **7a** formed from amide **6a** (see SI for details). Evaluation of the effect of temperatures and base showed that **7a** formed from **6a** in 88% yield with LiNCy_2 as the base instead of LiHMDS.

The scope of the α -arylation of secondary amides is illustrated by the examples in Table 5. Both electron-poor

Table 5. Scope for Pd-Catalyzed α -Arylation of Secondary Amides with Different ArBr^a

^aStandard condition as Table 1, entry 6, except for LiNCy₂ used as a base instead of LiHMDS. Isolated yield.

(**7b**, **7c**) and electron-rich aryl bromides (**7d**, **7e**) reacted in high yield (75–90%). Heteroaryl bromides, such as a bromo pyridine, benzothiophene and benzothiazole, reacted in good 70%, 79% and 89% yields, respectively (**7f–7h**). Like the α -arylation of carboxylic acids, the α -arylation of amides occurred with aryl bromides containing base-sensitive functional groups, such as acyl, alkoxy carbonyl and nitro groups, to give the product in 73–91% yield (**7i–7l**).

Studies on the scope of amides showed that a range of secondary amides underwent the α -arylation reaction. Amides derived from alkyl-, alkoxyalkyl- or aryl-substituted carboxylic acids and alkyl or aryl amines reacted to give the coupled product in 70–93% yield (**7m**, **7n**; **7p**, **7q**). Reaction of an amide containing an α -branched amino group occurred in a moderate 55% yield (**7o**). In this case, the installation of the

traceless protection occurred in approximately 84% yield, which is lower than for the less hindered amides, presumably due to the steric properties of the amino group. Like carboxylic acids, amides containing an N–H bonds and two alkyl groups on the α carbon did not react.

In summary, we have designed and implemented a strategy for the α -arylation of free carboxylic acids and secondary amides involving a traceless protecting strategy with a broad range of aryl and heteroaryl bromides in up to 99% yield. This coupling tolerates aryl bromides containing base-sensitive groups, such as acyl, alkoxy carbonyl, nitro, cyano and even hydroxyl groups. The value of this coupling was further illustrated by one-step syntheses of the five commercial Profen drugs Ibuprofen, Naproxen, Flurbiprofen, Fenoprofen and Ketoprofen in over 80% yield. Gram-scale preparations of a group of arylated carboxylic acids, including Naproxen and Flurbiprofen with 1–2 mol % palladium loading were achieved in one step in 72–87% yield. We hope that this method will be widely used for the direct synthesis of both synthetic intermediates and final products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b03291.

Experimental details and procedures, spectra for all unknown compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For reviews, see: (a) Miura, M.; Nomura, M. Direct Arylation via Cleavage of Activated and Unactivated C–H Bonds. *Top. Curr. Chem.* **2002**, 219, 211. (b) Lloyd-Jones, G. C. Palladium-Catalyzed α -Arylation of Esters: Ideal New Methodology for Discovery Chemistry. *Angew. Chem., Int. Ed.* **2002**, 41, 953. (c) Culkin, D. A.; Hartwig, J. F. Palladium-Catalyzed α -Arylation of Carbonyl Compounds and Nitriles. *Acc. Chem. Res.* **2003**, 36, 234. (d) Johansson, C. C. C.; Colacot, T. J. Metal-Catalyzed α -Arylation of Carbonyl and Related Molecules: Novel Trends in C–C Bond Formation by C–H Bond Functionalization. *Angew. Chem., Int. Ed.* **2010**, 49, 676. (e) Bellina, F.; Rossi, R. Transition Metal-Catalyzed Direct Arylation of Substrates with Activated sp³-Hybridized C–H Bonds and Some of Their Synthetic Equivalents with Aryl Halides and Pseudohalides. *Chem. Rev.* **2010**, 110, 1082. For initial work, see (f) Palucki, M.; Buchwald, S. L. Palladium-Catalyzed α -Arylation of Ketones. *J. Am. Chem. Soc.* **1997**, 119, 11108. (g) Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Direct α -Arylation of Ketones. Rate Acceleration by Sterically Hindered Chelating Ligands and Reductive Elimination from a Transition Metal Enolate Complex. *J. Am. Chem. Soc.* **1997**, 119, 12382. (h) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. Palladium-Catalyzed Regioselective Mono- and Diarylation Reactions

of 2-Phenylphenols and Naphthols with Aryl Halides. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740.

(2) Selected examples on palladium-catalyzed α -arylation of esters: (a) Carfagna, C.; Musco, A.; Sallese, G.; Santi, R.; Fiorani, T. Palladium-Catalyzed Coupling Reactions of Aryl Triflates or Halides with Ketene Trimethylsilyl Acetals. A New Route to Alkyl 2-Arylalkanoates. *J. Org. Chem.* **1991**, *56*, 261. (b) Moradi, W. A.; Buchwald, S. L. Palladium-Catalyzed α -Arylation of Esters. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (c) Lee, S.; Beare, N. A.; Hartwig, J. F. Palladium-Catalyzed α -Arylation of Esters and Protected Amino Acids. *J. Am. Chem. Soc.* **2001**, *123*, 8410. (d) Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. Efficient Synthesis of α -Aryl Esters by Room-Temperature Palladium-Catalyzed Coupling of Aryl Halides with Ester Enolates. *J. Am. Chem. Soc.* **2002**, *124*, 12557. (e) Liu, X.; Hartwig, J. F. Palladium-Catalyzed Arylation of Trimethylsilyl Enolates of Esters and Imides. High Functional Group Tolerance and Stereoselective Synthesis of α -Aryl Carboxylic Acid. *J. Am. Chem. Soc.* **2004**, *126*, 5182. (f) Hama, T.; Ge, S.; Hartwig, J. F. Palladium-Catalyzed α -Arylation of Zinc Enolates of Esters: Reaction Conditions and Substrate Scope. *J. Org. Chem.* **2013**, *78*, 8250. (g) Martin, A.; Vors, J.-P.; Baudoin, O. Synthesis of Conformationally Constrained Esters and Amines by Pd-Catalyzed α -Arylation of Hindered Substrates. *ACS Catal.* **2016**, *6*, 3941.

(3) Selected examples on palladium-catalyzed α -arylation of amides: (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Inter- and Intramolecular α -Arylation of Amides. Application of Intramolecular Amide Arylation to the Synthesis of Oxindoles. *J. Org. Chem.* **1998**, *63*, 6546. (b) Cossy, J.; de Filippis, A.; Pardo, D. G. Palladium-Catalyzed Intermolecular α -Arylation of *N*-Protected 2-Piperidinones. *Org. Lett.* **2003**, *5*, 3037. (c) Hama, T.; Culkin, D. A.; Hartwig, J. F. Palladium-Catalyzed Intermolecular α -Arylation of Zinc Amide Enolates under Mild Conditions. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (d) Wu, L.; Falivene, L.; Drinkel, E.; Grant, S.; Linden, A.; Cavallo, L.; Dorta, R. Synthesis of 3-Fluoro-3-aryl Oxindoles: Direct Enantioselective α -Arylation of Amides. *Angew. Chem., Int. Ed.* **2012**, *51*, 2870.

(4) (a) Harrington, P. J.; Lodewijk, E. Twenty Years of Naproxen Technology. *Org. Process Res. Dev.* **1997**, *1*, 72. (b) Neumann, H.; Brennfürer, A.; Beller, M. An Efficient and Practical Sequential One-Pot Synthesis of Suprofen, Ketoprofen and Other 2-Arylpropionic Acids. *Adv. Synth. Catal.* **2008**, *350*, 2437. (c) Taylor, E. C.; Katz, A. H.; Alvarado, S. I.; McKillop, A. Thallium in Organic Synthesis. 65. A Novel Synthesis of Benzoxazoles from Anilides. *J. Org. Chem.* **1986**, *51*, 1607. (d) Terada, A.; Naruto, S.; Wachi, K.; Tanaka, S.; Iizuka, Y.; Misaka, E. J. Synthesis and Antiinflammatory Activity of [(Cycloalkylmethyl)phenyl]acetic Acids and Related Compounds. *J. Med. Chem.* **1984**, *27*, 212. (e) Imai, M.; Ishikura, M. Preparation of Pranoprofen. Jpn. Kokai Tokkyo Koho 62258382, 1987. (f) Takeda, H.; Morifuji, N.; Takahashi, T. Preparation of 2-(10,11-Dihydro-10-oxodibenzo-[b,f]thiepin-2-yl)propionic Acid as an Inflammation Inhibitor and Analgesic. Jpn. Kokai Tokkyo Koho 62292780, 1987.

(5) (a) Bala, T.; Prasad, B. L. V.; Sastry, M.; Kahaly, M. U.; Waghmare, U. V. Interaction of Different Metal Ions with Carboxylic Acid Group: a Quantitative Study. *J. Phys. Chem. A* **2007**, *111*, 6183. (b) Pichette Drapeau, M.; Gooßen, L. J. Carboxylic Acids as Directing Groups for C–H Bond Functionalization. *Chem. - Eur. J.* **2016**, *22*, 18654. (c) Sigel, H.; Martin, R. B. Coordinating Properties of the Amide Bond. Stability and Structure of Metal Ion Complexes of Peptides and Related Ligands. *Chem. Rev.* **1982**, *82*, 385.

(6) Morita, Y.; Yamamoto, T.; Nagai, H.; Shimizu, Y.; Kanai, M. Chemoselective Boron-Catalyzed Nucleophilic Activation of Carboxylic Acids for Mannich-Type Reactions. *J. Am. Chem. Soc.* **2015**, *137*, 7075.

(7) For reviews, see: (a) Hartwig, J. F. Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564. For selected examples, see (c) Yin, J.; Buchwald, S. L.

Palladium-Catalyzed Intermolecular Coupling of Aryl Halides and Amides. *Org. Lett.* **2000**, *2*, 1101. (d) Shen, Q.; Hartwig, J. F. Lewis Acid Acceleration of C–N Bond-Forming Reductive Elimination from Heteroaryl palladium Complexes and Catalytic Amidation of Heteroaryl Bromides. *J. Am. Chem. Soc.* **2007**, *129*, 7734. (e) Becica, J.; Dobereiner, G. E. Acceleration of Pd-Catalyzed Amide *N*-Arylations Using Cocatalytic Metal Triflates: Substrate Scope and Mechanistic Study. *ACS Catal.* **2017**, *7*, 5862. (f) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. Breaking the Base Barrier: an Electron-Deficient Palladium Catalyst Enables the Use of a Common Soluble Base in C–N Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 4721.

(8) (a) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. Two Methods for Direct ortho-Arylation of Benzoic Acids. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (b) Wu, G.-J.; Guan, J.; Han, F.-S.; Zhao, Y.-L. Palladium-Catalyzed Silver-Mediated α -Arylation of Acetic Acid: A New Approach for the α -Arylation of Carbonyl Compounds. *ChemCatChem* **2014**, *6*, 1589. (c) Tanaka, D.; Tanaka, S.; Mori, A. Palladium-Catalyzed α -Arylation of Carboxylic Acid Derivatives with Grignard Reagent. *Eur. J. Org. Chem.* **2014**, *2014*, 4254. (d) Sha, S.-C.; Zhang, J.; Walsh, P. J. Palladium-Catalyzed α -Arylation of Aryl Acetic Acid Derivatives via Dienolate Intermediates with Aryl Chlorides and Bromides. *Org. Lett.* **2015**, *17*, 410.

(9) (a) Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. Orthogonal Pd- and Cu-Based Catalyst Systems for C- and N-Arylation of Oxindoles. *J. Am. Chem. Soc.* **2008**, *130*, 9613. (b) Xiao, Z.-K.; Yin, H.-Y.; Shao, L.-X. *N*-Heterocyclic Carbene-Palladium (II)-1-Methylimidazole Complex Catalyzed α -Arylation of Oxindoles with Aryl Chlorides and Aerobic Oxidation of the Products in a One-pot Procedure. *Org. Lett.* **2013**, *15*, 1254.

(10) Ahmadi, A.; Danialia, M.; Kazemia, S.; Azamia, S.; Alizadea, N. Synthesis of Ibuprofen with Modified and Economical Process as an NSAID Drug. *J. Appl. Chem. Res.* **2014**, *8*, 91.